REMARKS/ARGUMENTS

Status of the claims

With entry of the instant amendment, claim 137 is amended. This amendment adds no new matter and changes "t(9;22)(q11;q34)" to read "t(9;22)(q34;11)". Support can be found in the specification, *e.g.,* at page 14, lines 21-25.

The Examiner rejoined claims 150 and 151. Claims 127, 128, 130-134, 136-142, and 146-155 are therefore pending and under examination.

Application relationship to parent

The Examiner indicates that no restriction requirement was made in parent application no. 08/487,974 and that the priority claim assertion that this is a divisional application is improper. Enclosed herewith is a Supplemental Application Data Sheet that has been amended to indicate that the present application is a continuation of application no. 08/487,974.

Correction to drawings

Applicants are in the process of trying to obtain color photographs from the parent application files and intend to provide the three sets of color drawings, petition under 37 CFR 1.84(a)(2), and amend the specification at the brief description of the drawings to include the required language relating to the color drawings.

Rejection under 35 U.S.C. § 112-second paragraph

Claim 137 is rejected as allegedly indefinite over the recitation of the chromosomal translocation designation t(9;22)(q11;q34). Applicants have amended the claim to recite "t(9;22)(q34;q11)" to correct the typographical error. It is therefore requested that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103

First, the Examiner alleges that claims 132-134, 136-142, 146, 147 and 149 include additional limitations that refer to intended hybridization targets of the claimed composition. The Examiner believes that the use of the probes does not limit the structure and therefore alleges that the intended use limitations in the noted claims do not have patentable weight. Although Applicants' disagree with the Examiner's legal analysis, the comments are not addressed in this paper because the Examiner indicated that the limitations were considered during examination.

Rejection of claims 127, 128, 130-134, 136, 139-141, 148, and 149

Claims 127, 128, 130-134, 136, 139-141, 148, and 149 are rejected as allegedly obvious over Bartram *et al.*, *The EMBO J.* 4:683-686, 1985 ("Bartram") over Hopman *et al.*, *Histochemistry* 85:1-4, 1986 ("Hopman") in view of Hariharan *et al.*, *The EMBO J.* 6:115-119, 1987 ("Hariharan"), in view of Shtivelman *et al.*, *Cell* 47:277-284, 1986 ("Shtivelman") in view of Lawrence e*t al.*, *Cell* 52:51-61, 1988 ("Lawrence"). The Examiner characterizes Bartram as showing *in situ* hybridization to metaphase chromosomes from a patient having a complex chromosomal translocation between chromosomes 9, 22, and 12 using radio-labeled ABL and BCR probes that hybridize to translocated regions of the chromosomes. Hopman is generally characterized in the rejection as showing double-label fluorescence *in situ* hybridization using total human DNA and mouse repetitive sequences labeled with different labels; and as noting that simultaneous non-radioactive double hybridization may be useful for high resolution detection of relative positions of two genes in normal and abnormal karyotypes. Hariharan and Shtivelman are cited in the Office Action as allegeldy teaching maps/sequences of the BCR and ABL genes, respectively, and maps of the rearranged ABL-BCR fusion of the Philadelphia chromosome (Hariharan). Lawrence is described in the rejection as teaching use of a fluorescent probe to detect a single copy sequence and as teaching that fluorescent probes provide for higher resolution. The Examiner alleges that one of skill would have been motivated to combine the teachings of these references in view of Lawrence's description of fluorescent probes to detect single copy sequence in metaphase and interphase cells and the advantages of using fluorescent

probes relative to radio-labeled probes; and thus, according to the Examiner, would have arrived at Applicants' invention. Applicants respectfully traverse this rejection.

As noted by the Examiner, Bartram fails to describe or suggest double-label fluorescence *in situ* hybridization using single copy probes, or the other elements of various claims that are noted on page 7, paragraph 2 of the Office Action. Although Hopman employs two probes, each labeled with a distinguishable label, the target sequences were highly repeated (see, e.g., page 3 of Hopman). Hopman notes that middle and low repeated sequences are within the sensitivity of these techniques, but does not provide any teachings relating to detection of translocation that involve specific genes. Hopman provides no teachings or evidence that would lead to the conclusion that two probes, each labeled with a distinguishable label, where one probe hybridizes to the ABL gene side of said chromosomal aberration and the other of said probes hybridizes to the BCR gene side, could successfully be used to detect a Philadelphia chromosome translocation. Furthermore, Hopman fails to provide any evidence that doublets resulting from the signals generated from probes having properties recited in the current claims could be generated.

Lawrence is cited in the rejection as teaching detection of a single copy sequence using a fluorescent probe; however, Lawrence is detecting an EBV genome that is integrated into chromosome 1 in a human cell line. Lawrence does not detect human chromosome sequences. Lawrence in fact notes that with regard to determining the spatial orientation of the EBV sequences that "interpretations of our results must take into consideration the possibility that the integrated viral genome exhibits less condensation than the rest of the chromosomal DNA" (page 88, column 2, lines 9-13).

Hariharan is cited in the rejection as showing maps of the BCR gene, maps of the rearranged ABL-BCR fusion of the Philadelphia chromosome and the sequence of the BCR gene. However, Hariharan does not teach analysis of the genomic BCR gene or of the genomic ABL-BCR fusion. Hariharan analyzed the structure of the BCR cDNA by identifying clones in a cDNA library prepared from poly(A)+ RNA from a cell line (see, page 115, first paragraph under "**Results**"). The map in Figure 1 relates to the human bcr cDNA clones, not the bcr gene. The Figure merely shows four *bcr* cDNA clones (see, p. 115, column 2, second full paragraph).

Hariharan hybridized to transcripts, not genomic DNA in chromosomes (see, page 118). Hariharan does not provide the sequence of the BCR gene in Figure 2 (it is the cDNA sequence; see, the figure legend). At most, Hariharan teaches a single partial probe. The rejection provides no evidence that such a probe would be useful in the claimed methods. Hariharan thus provides no teachings that would make obvious BCR and ABL probes of any desired portions of the genes to study Philadelphia chromosomes.

Shtivelman is described in the rejection as discussing the correlation between chronic myeloid leukemia and the Philadelphia chromosome, and as showing a map of the ABL gene and the sequence in Figure 1. Shtivelman discloses the primary structure of the normal abl protein by sequencing the abl cDNA (see, abstract). Shtivelman further characterizes two alternative first exons and the promoter regions for the alternative exons (p. 278-280). Shtivelman additionally characterizes the *bcr-abl* fusion RNA in the KC1-22 cell lines (p. 281). Shtivelman's teachings relating to genomic DNA are thus in fact limited to characterization of the alternative promoters. Shtivelman therefore provides no teachings or suggestions relating to probes that can be successfully used in the methods of the invention.

The Supreme Court has "warn[ed] against 'temptation to read into the prior art the teachings of the invention in issue' and instruct[ed] courts to 'guard against slipping into the use of hindsight.'" *KSR Int'l v. Teleflex Inc.,* 127 S.Ct 1742 (2007), quoting *Graham v. John Deere Co., supra,* at 36. Here, it is only Applicants' disclosure that provides the basis for developing a combination of probes as recited in the current claims.

Rejection of claim 127, 132-134, 136-138, 146, and 147

Claims 127, 132-134, 136-138, 146, and 147 are rejected for the reasons noted above and additionally, further in view of Ribeiro *et al., Blood* 70:948-953, 1987 ("Ribeiro"). The Examiner contends that it would have been obvious to make probes for analyzing ABL-BCR junctions in view of the references discussed above that would detect Philadelphia chromosomes having a t(9;22)(q34;11) translocation because Ribeiro shows that the Philadelphia chromosome correlates with CLL. Applicants respectfully disagree. As explained above, one of skill would not have made the claimed composition because there was no expectation that the two probes

could in fact be used in combination to identity the Philadelphia chromosome translocation. Ribeiro provides no additional teachings that would suggest that the claimed composition would have been made by one of skill in the art, as there would be no use for such a composition in the absence of Applicants' disclosure. Accordingly, the claims are patentable over the combination of cited references, including Ribeiro.

Rejection of claims 127, 132, and 142

Claims 127, 132, and 152 are additionally rejected over the combination of Bartram, Hopman, Hariharan, Shrivelman and Lawrence as described above and further in view of Selden *et al., Proc. Natl. Acad. Sci USA*80:7289-7292, 1983 ("Selden"). The Examiner describes Selden as showing use of *in situ* hybridization to analyze an altered Philadelphia chromosome in a cell line, and as using an ABL probe as part of the analysis. The Examiner contends that it would have been obvious to makes probes for analyzing ABL-BCR junctions that would detect a Philadelphia chromosome in a cell line because Selden shows that cell lines may be used in *in situ* hybridization to study chromosomal rearrangements in Philadelphia chromosomes. Applicants additionally traverse this rejection.

Selden merely describes analysis of a cell line for a Philadelphia chromosome. One of skill would not have developed a composition comprising probes as set forth in claims 127, 132, and 152 based on Selden's description. The claimed probes are labeled with distinguishable labels and have the properties such that one probe binds to the BCR side of a translocation and the other probe binds to the ABL side. The combination of Bartram, Hopman, Hariharan, Shtivelman and Lawrence would not lead one of skill in the art to make this particular composition for the reasons discussed above. Selden does not compensate for these deficiencies.

Rejection of claims 127, 128, 148, 151, 152, and 154

Claims 127, 128, 148, 151, 152, and 154 are rejected as allegedly obvious over Bartram in view of Hopman in view of Hariharan in view of Shtivelman in view of Lawrence as described above and further in view of Lau *et al., Proc. Natl. Acad. Sci* USA 80:5225-5229, 1983 ("Lau") as evidenced by Westbrook, U.S. Patent No. 6,575,421. The Examiner contends

that the claimed compositions are obvious because it would have been obvious to use a probe based on the cosmid vector of Lau. Applicants respectfully traverse. As explained above, the combined disclosure of Bartram, Hopman, Hariharan, Shtivelman, and Lawrence do not result in Applicants' invention. Lau provides no additional disclosure that compensates for the deficiencies of the primary references.

Rejection of claims 127, 128, 148, 150, 153, and 155

Claims 127, 128, 148, 150, 153, and 155 are rejected as allegedly obvious over Bartram in view of Hopman in view of Hariharan in view of Shtivelman in view of Lawrence as described above and further in view of Frischauf *et al., J. Mol. Biol* 170:827-842, 1983 ("Frischauf") as evidenced by Westbrook, U.S. Patent No. 6,575,421. The Examiner contends that the claimed compositions are obvious because it would have been obvious to use a probe based on the EMBL3 vector of Frischauf. Applicants respectfully traverse. As explained above, the combined disclosure of Bartram, Hopman, Hariharan, Shtivelman, and Lawrence do not result in Applicants' invention. Frischauf provides no additional disclosure that compensates for the deficiencies of the primary references.

In view of the foregoing, the Examiner has not established that the claims are *prima facie* obvious over the cited references. Applicants therefore respectfully request withdrawal of all of the rejections under 35 U.S.C. § 103.

Double patenting

The Examiner notes that should claim 127 be allowable, claims 128 and 148 will be objected to as being a substantial duplicate thereof. Applicants will address this once claim 127 has been determined to be allowable.

Obviousness-type double patenting

Claims 127, 128, 130, 131, and 148 are rejected for alleged obviousness-type double patenting over claims 3 and 11 of U.S. Patent No. 6,280,929.

Claims 127, 128, 130, 131, and 148 are provisionally rejected for alleged obviousness-type double patenting over claims 23, 24, 38, 72, 74, 118, 122, and 123 of co-pending Application No. 10/608,092.

Claims 127, 128, 130, 134, 136-142, 146-148, and 150-155 are rejected for alleged obviousness-type double patenting over claims 3, 7, 8, 10-16, 19, 21, 22, 24, and 26-36 of U.S. Patent No. 6,576,421.

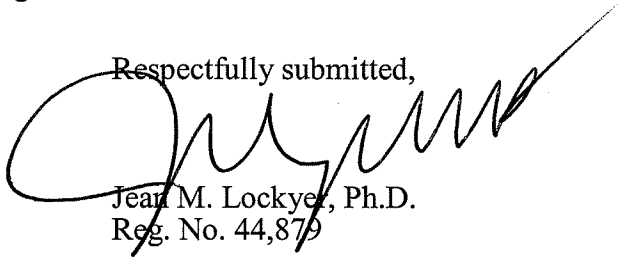
Applicants have noted the obviousness-type double patenting rejections. Applicants respectfully request that the Examiner hold these rejections in abeyance until there is an indication of allowable subject matter in the instant application.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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